Section 5

The Blood and Spleen

APLASTIC ANEMIA

method of
MANJUSHA KUMAR, M.D., and
BLANCHE P. ALTER, M.D.
University of Texas Medical Branch at Galveston
Galveston, Texas

Aplastic anemia (AA) is characterized by peripheral blood pancytopenia and reduced or absent production of blood cells in the marrow. The disorder is rare and may be acquired (2 to 6 per million per year) or inherited, as in Fanconi's anemia (>1000 cases reported, incidence unknown) (Table 1). The clinical severity of acquired AA is important for prognosis and treatment decisions. In severe aplastic anemia (SAA), the patient has at least two of the following findings: a granulocyte count lower than 500 per mm^3, a platelet count lower than 20,000 per mm^3, and a corrected reticulocyte count of less than 1% (40,000 per mm^3), in addition to less than 25% cellularity on the bone marrow biopsy or moderate hypocellularity in which less than 30% cells are hematopoietic. Very severe aplastic anemia (VSAA) patients have absolute granulocyte counts of less than 200 per mm^3.

Mild or moderate AA, also called *hypoplastic anemia*, has a variable and arbitrary definition in the literature and may be defined according to one of the following:

1. AA that does not meet criteria for severe disease.
2. Bone marrow hypocellularity with all of the following: an absolute neutrophil count (ANC) lower than 2500 per mm^3, a platelet count lower than 120,000 per mm^3, and a hematocrit of less than 38%.
3. At least 2 of the following: an ANC lower than 1500 per mm^3, a platelet count lower than 40,000 per mm^3, and an absolute reticulocyte count lower than 40,000 per mm^3.

Many cases of acquired AA appear to result from immune-mediated destruction of marrow cells. A variety of factors, such as drugs, viruses, pregnancy, thymomas and graft versus host disease (GVHD), can activate the immune system, leading to marrow aplasia. Another pathogenetic mechanism of AA is direct marrow stem cell damage from agents such as chemotherapeutic drugs, radiation therapy, and benzene. In most cases, however, no associated factor can be identified, and the patient is said to have *idiopathic aplastic anemia*.

TABLE 1. **A Classification of Aplastic Anemia**

Acquired Aplastic Anemia	Inherited Aplastic Anemia
Secondary Aplastic Anemia	Fanconi's anemia
Radiation	Dyskeratosis congenita
Drugs and chemicals	Shwachman-Diamond syndrome
Regular effects: cytotoxic agents, benzene	Reticular dysgenesis
Idiosyncratic reactions	Amegakaryocytic thrombocytopenia
Chloramphenicol	Familial aplastic anemias
Nonsteroidal anti-inflammatory drugs	Preleukemia (e.g., monosomy 7)
Antiepileptics, gold	Nonhematologic syndromes (Down's, Dubovitz's, Seckel's)
Other drugs and chemicals	
Viruses	
Epstein-Barr virus (infectious mononucleosis)	
Non-C (non-A, non-B) hepatitis	
Human immunodeficiency virus (acquired immunodeficiency syndrome)	
Immune diseases	
Eosinophilic fasciitis	
Hypoimmunoglobulinemia	
Thymoma and thymic carcinoma	
Graft-versus-host disease	
Paroxysmal nocturnal hemoglobinuria	
Pregnancy	
Idiopathic Aplastic Anemia	

From Young NS, Alter BP: Aplastic Anemia: Acquired and inherited. Philadelphia, W.B. Saunders Co., 1994, p 9.

CLINICAL AND LABORATORY FEATURES

The clinical manifestation is related to the severity of the underlying pancytopenia. Hemorrhagic symptoms from thrombocytopenia are usually the first manifestations of the disease. Fever, mouth sores, and fulminant sepsis can result from severe neutropenia. Severe anemia can lead to fatigue, palpitations, and shortness of breath, but often occurs late in the course of the disease because the life span of the erythrocyte (120 days) far exceeds those of platelets (10 days) and granulocytes (7 hours).

Laboratory findings are nonspecific; the peripheral smear reveals a paucity of platelets and leukocytes but normal red blood cell morphology. The anemia may be macrocytic or normocytic. The absolute reticulocyte count is decreased. Increases in fetal hemoglobin and red blood cell i antigen along with macrocytosis are manifestations of the fetal-like erythropoiesis seen in stress hematopoiesis and may be seen in long-standing aplasia. Results of the Ham or sucrose lysis test may be positive, as paroxysmal nocturnal hematuria may be associated with AA. Flow cytometric analysis of red and white blood cells for the presence of cell surface markers CD55 and CD59 (deficient glycophosphoinositol-linked protein expression) is a more sensitive and objective method for investigation of paroxysmal nocturnal hemoglobinuria in patients with AA. Peripheral blood chromosomes are normal, in contrast to increased breakage with clastogenic agents in patients with Fanconi's anemia. Vitamin B_{12} and folate levels are normal.

Serum transaminase levels may be high in patients with hepatitis, and viral serologic studies for hepatitis A, B, and C viruses, Epstein-Barr virus, cytomegalovirus (CMV), parvovirus, and human immunodeficiency virus (HIV) may be helpful. Bone marrow aspiration and biopsy are useful for exclusion of other causes of pancytopenia (metastatic tumors, leukemia, granulomatous disease). The marrow cellularity is poor (<25%) with empty spicules, fat, reticulum cells, plasma cells, and mast cells. Sometimes a lymphocytic infiltration of the marrow is observed and correlates with poor prognosis if more than 70% of marrow cells are lymphocytes. Bone marrow cytogenetic findings are usually normal, thus excluding myelodysplastic syndrome.

THERAPY

Treatment of AA involves (1) specific therapy aimed at curing the disease and (2) ongoing supportive care to prevent complications of pancytopenia and its treatment. The choice of therapy depends on the severity of the disease and the age of the patient (Figure 1). Spontaneous recovery can also occur and has been reported anecdotally.

Bone Marrow Transplantation

In patients less than 40 years of age with newly diagnosed SAA, an urgent HLA typing of the patient's and first-degree relatives' lymphocytes should be instituted. There is a 25 to 30% probability of finding a fully compatible family member donor. Allogeneic bone marrow transplantation (BMT) from a fully HLA-matched related donor offers the best chance of cure of this disease (60 to 70% survival rates). Conditioning regimens for BMT currently involve non–radiation-based therapy: cyclophosphamide (Cytoxan), 50 mg per kg per day on days −5, −4, −3 and −2, in combination with antithymocyte globulin (Atgam), 30 mg per kg per day on days −5, −4, and −3 given 12 hours after the infusion of Cytoxan on each of these days. In patients younger than 20 years, survival rates higher than 90% are being achieved with current supportive care techniques and better GVHD prophylaxis in allogeneic BMT for SAA.

In the absence of a fully compatible related donor, other transplantation possibilities are blood from an unrelated matched donor, blood from a partially mismatched related donor, and matched or partially mismatched, related or unrelated umbilical cord blood. Each of these involves a higher risk of graft rejection, severe GVHD, and increased risks of morbidity and mortality. Results with unrelated donor transplants have been discouraging for these reasons, and survival rates are less than 30% in most series. Thus at this time it does not appear justified to offer a patient these alternative modalities of BMT as a treatment of first choice. Older patients (older than 40 years) appear to suffer significant toxic effects and GVHD from allogeneic BMT even with a sibling matched transplant; survival rates are 40 to 45%. Other treatments such as immunosuppression therefore offer

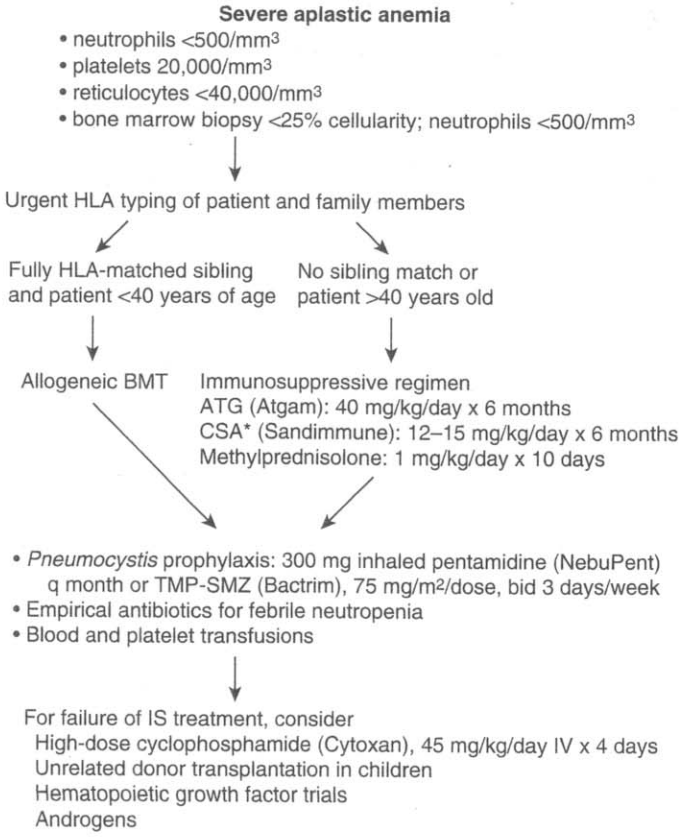

Figure 1. Approach to the management of aplastic anemia. *Abbreviations:* ATG = antithymocyte globulin; CSA = cyclosporine; IS = immunosuppressive. *Not FDA approved for this indication.

them a better chance of remission with significantly lower rates of morbidity and mortality.

Immunosuppressive Therapy

Several immunosuppressive regimens have achieved varying success in the treatment of AA, which suggests that this may be an immune-mediated disease. The most potent immunosuppressive regimen appears to be a combination of antithymocyte globulin (ATG) or antilymphocyte globulin (ALG) with cyclosporine* (Sandimmune) and methylprednisolone. This offers a 70% chance of response/remission and should be offered as first-line therapy to patients without a sibling matched donor for BMT and to those older than 40 years with SAA. We treat as per the National Institutes of Health (NIH) guidelines: ATG at 40 mg per kg per day† for 4 days and cyclosporine at 12 mg per kg per day in adults and 15 mg per kg per day in children, orally for 6 months. The dose of cyclosporine is adjusted to maintain serum levels of 200 to 400 ng per mL by radioimmunoassay. Subsequently cyclosporine is tapered slowly and discontinued over 5 months. Methylprednisolone, 1 mg per kg per day, is given for 10 days and tapered over 2 weeks. A test dose of 10 microliters of undiluted ATG (50 mg per mL) is given subcutaneously as a sensitivity test. Immunosuppressive treatment may ameliorate the disease and help the patient become transfusion independent and free of recurrent neutropenic infections. Rarely, however, is there a complete response with normalization of peripheral blood counts and bone marrow. There is a significant risk of development of clonal disease such as paroxysmal nocturnal hemoglobinuria, myelodysplastic syndrome, or acute myeloid leukemia (probability of clonal evolution is calculated to be 50% at 10 years).

Side effects of this regimen include anaphylaxis, urticaria, fever, chills, thrombocytopenia, and serum sickness from ATG. Cyclosporine may cause renal dysfunction, hypomagnesemia, hypertension, and neurotoxicity.

Another immunosuppressive regimen that has been shown to be promising in a small pilot study is high-dose cyclophosphamide. This is a potent immunosuppressive and cytotoxic drug and is used as conditioning preparation for BMT. Cyclophosphamide at 45 mg per kg per day for 4 days induced remission in 7 of 10 patients with SAA with a median follow up of more than 10 years. The beneficial effect of cyclophosphamide may be by potent immunosuppression and hence autologous recovery. Although these results appear promising, larger studies are needed to define the exact role and hierarchy of cyclophosphamide in the treatment of AA.

Transfusion Support

Patients with AA need frequent transfusions of blood and platelets during treatment whether therapy is by BMT or immunosuppression. In addition, patients in whom all treatment modalities have failed need long-term transfusion support. Some key points in transfusing these patients are as follows:

- No family member should be used as a source of blood products if the patient with AA is a potential BMT candidate. This is to decrease the risk of alloimmunizations from minor histocompatibility antigens, which may impair the transplantation outcome (increased risk of rejection).
- To further decrease the risk of alloimmunization and possible graft rejection in transplantation candidates, these patients should undergo transfusion as little as possible. General guidelines are to transfuse for hemoglobin of less than 7 grams per dL or if the patient is symptomatic with tachycardia, lethargy, and subjective symptoms at higher hemoglobin values. Platelets should be given prophylactically for levels lower than 10,000 per mm^3 in stable, nonfebrile patients.
- All blood products should be leukocyte-poor, irradiated, and CMV negative if the patient is CMV negative and is a potential transplantation candidate.
- Single donor platelets should be used as much as possible to decrease the exposure to multiple donors and decrease the risk of alloimmunization.

Infection Support

Patients receiving immunosuppressive regimens and undergoing BMT should receive *Pneumocystis carinii* prophylaxis, preferably with a nonmyelosuppressive agent such as pentamidine (NebuPent), 300 mg by inhalation once a month. In younger patients, trimethoprim-sulfamethoxazole (Bactrim, Septra) is used for prophylaxis (75 mg per m^2 per dose of trimethoprim, twice a day, 3 consecutive days a week). There is no role for other antibiotic prophylaxis in these neutropenic patients during the baseline state. With a febrile neutropenic episode (granulocyte count < 500 per mL), empirical broad-spectrum antibiotics should be started until infection is ruled out and the patient is afebrile. Several antibiotics have been used as either monotherapy or combination therapy for the initial fever. Important bacteria to be covered are the endogenous flora of the gastrointestinal tract such as *Escherichia coli*, *Pseudomonas* species, *Klebsiella* species, and anaerobic organisms. Both ceftazidime (Fortaz), a third-generation cephalosporin, and imipenem will cover any life-threatening gram-negative bacilli, especially *Pseudomonas,* and have been used as monotherapy. If a line infection is suspected, vancomycin (Vancocin) should be started empirically to cover any present coagulase-negative staphylococci. Anaerobic coverage with clindamycin (Cleocin) may need to be initiated if there are mouth sores or a perianal abscess. Depending on the type of organism in the blood culture, if any, the antibiotic therapy and duration may be changed accordingly. In patients who have a prolonged fever (>1 week) and are unresponsive to broad-spectrum antibiotics (covering

*Not FDA approved for this indication.
†Exceeds dosage recommmended by the manufacturer.

for gram-positive and gram-negative bacteria), especially if they have central lines, have mucocutaneous breaks, or have received prior antibiotics, empirical systemic antifungal therapy should be started with amphotericin B (Fungizone) while fungal cultures are examined.

Hematologic Growth Factors

Granulocyte colony-stimulating factor (G-CSF) (Neupogen) is commonly used in subcutaneous doses of 5 to 10 μg per kg per day in patients with AA during a febrile neutropenic episode, especially if they are very sick. It is also used to shorten the period of neutropenia in patients who have undergone transplantation. However, the sole use of growth factors as front-line therapy for treatment of newly diagnosed SAA offers no definite long-term benefit to the patient and may delay curative therapy. Because there is no established alternative treatment for patients who are not candidates for BMT and are primarily nonresponsive to ATG plus cyclosporine, growth factors have been used in phase I/II trials alone, in combination with immunosuppressive therapy, or as a combination of hematopoietic growth factors. There are reports of treatment of refractory AA with G-CSF, G-CSF plus immunosuppressive agents, granulocyte-macrophage colony-stimulating factor (GM-CSF), stem cell factor,* interleukin-3 (IL-3),* interleukin-1,† erythropoietin plus G-CSF, and erythropoietin alone. Responses are transient, monolineage, and generally limited to patients with nonsevere AA.

For patients with moderate AA who are transfusion independent, the "watch and wait" policy holds. Most patients with moderate AA require no therapy or minimal short-term transfusion support. In some patients in whom disease advances to SAA, the treatment is as detailed earlier for SAA.

Miscellaneous Treatments

Androgens no longer have a primary role in the management of AA unless all of the therapies discussed earlier are unavailable (as in several underdeveloped countries) or unsuccessful. Androgens may increase erythropoietin production, stimulate erythroid progenitor cells, and increase hemoglobin levels. The usual oral androgen is oxymetholone (Anadrol-50), 2 to 5 mg per kg per day, or nandrolone decanoate* (Deca-Durabolin), 5 mg per kg per week intramuscularly. Cholestatic jaundice and hepatomegaly can result, along with some masculinizing effects. Hepatic tumors are a serious risk, and liver function tests and abdominal ultrasonography should be performed for monitoring.

Splenectomy is currently done to facilitate supportive care when there is evidence of hypersplenism impacting on platelet and red blood cell transfusions. In the past it had been used as a treatment modality for AA with occasional responses, but the risk of surgery, bleeding, and infection is difficult to justify.

In anecdotal reports, *plasmapheresis* and *lymphocytapheresis* ameliorated the disease, perhaps by removing immunoglobulins or soluble inhibitory factors and circulating lymphocytes.

Pooled human *immunoglobulin** at 0.4 mg per kg for 4 days every 3 weeks has rarely produced transient remission in this disease.

Antiviral treatment with acyclovir may result in temporary responses, perhaps because of the association of AA with viral infections (see Table 1). However, viral infection has not been documented in anecdotal reports of patients with AA who responded to acyclovir.

Lithium, a drug used in manic-depressive patients, can cause neutrophilia. There are rare reports of remissions in patients with AA.

Phytohemagglutinin, a plant lectin, was given intravenously in 6 patients with AA and ameliorated symptoms.

*Investigational drug in the United States.
†Not FDA approved for this indication.

FANCONI'S ANEMIA

Fanconi's anemia (FA) is one of the important inherited causes of aplastic anemia and pancytopenia primarily but not exclusively in the pediatric age group. It is an autosomal recessive disease with at least eight complementation groups. Three of the FA genes have been cloned (FAC, FAA, and FAG), and a fourth (FAD) has been mapped but not yet cloned.

Clinical and Laboratory Features

FA was initially identified as an association between AA and a specific constellation of birth defects: hyperpigmentation and/or café au lait spots, short stature, and anomalies of the thumb and radius in more than half of affected patients. Other, less common physical stigmata are male hypogonadism, microcephaly, ocular and renal abnormalities, developmental delay, low birth weight, defects of the ear and lower limbs, and occasionally cardiopulmonary defects. However, up to one third of patients may not have birth defects, and hence it is important to rule out Fanconi's anemia in the work-up of all patients with AA.

Useful radiologic studies include skeletal radiographs, which may identify both obvious and occult abnormalities, and renal ultrasonography, to identify structural kidney defects.

The hematologic findings in FA are quite nonspecific; they begin to manifest at an average age of 8 to 9 years, but time of onset ranges from birth to the sixth decade. Patients commonly come to medical attention with thrombocytopenia or macrocytic anemia, which then advances to pancytopenia. Bone marrow appearances vary but generally are hypocellular with reduced or absent megakaryocytes. At

*Not FDA approved for this indication.

least 10% of patients with FA develop leukemia (usually myeloid), and acute myeloid leukemia may be the first presentation in some FA patients. Myelodysplastic syndrome is also seen frequently.

The diagnostic laboratory test entails the use of metaphase preparations of phytohemagglutin-stimulated cultured peripheral blood lymphocytes. A high proportion of cells from FA patients have breaks, gaps, rearrangements, exchanges, and endo-reduplications. This breakage is dramatically increased in comparison to normal samples when clastogenic agents such as diepoxybutane or mitomycin C are added.

Therapy

Approximately 1000 patients with FA have been described in the literature. Because of improvements in supportive care in the 1990s, the median length of survival of patients with FA is projected to be more than 30 years. The major immediate causes of death are complications of pancytopenia: bleeding, fulminant sepsis, and, less frequently, malignancy (acute myeloid leukemia, liver tumors, squamous cell carcinomas). The same principles of transfusion support and infection control apply to these patients as for those with idiopathic AA. Hematopoietic growth factors (G-CSF, GM-CSF, IL-3) have shown some response in these patients in small pilot studies, but they are not yet standards of care in FA.

Androgens. About 50% of patients respond to androgen therapy, and we usually begin administering androgens when the platelet count is consistently below 30,000 per mm^3 and/or the hemoglobin is less than 7 grams per dL. Responses usually begin with reticulocytosis, with a rise in hemoglobin within 1 to 2 months. White blood cell counts increase next, although often inadequately; the platelet count rise is usually incomplete and, at androgren dosages of 2 to 5 mg per kg per day, may take 6 to 12 months to reach its maximum. Oxymetholone is most frequently used. Prednisone has been included at 5 to 10 mg every other day to possibly enhance the effect of androgens on the marrow, to counteract the growth acceleration of androgens, and to perhaps increase vascular stability.

Bone Marrow Transplantation. BMT currently offers the only possibility for cure of aplastic anemia in FA. Patients wth FA are very sensitive to alkylating agents and radiation therapy because of their DNA instability. Thus the standard cyclophosphamide and total body irradiation conditioning regimen has to be modified in FA patients, usually reduced to 20 mg per kg of cyclophosphamide over 4 days plus 5 Gy of thoracoabdominal irradiation. Survival rates are higher than 70% with a matched sibling donor transplant. It is mandatory to test the donor sibling for FA because this is an autosomal recessive disorder and not all patients may exhibit phenotypic features. Secondary cancers may develop in patients with FA because of their inherent risk and because of potentiation of the risk by immunosuppression for transplantation. For patients without a fully matched related donor, alternative donor transplants offer poor results. FA is now being diagnosed in adults with typical solid tumors, infertility, or late-onset aplastic anemia and should be considered in the evaluation of anyone with bone marrow failure at any age.

DYSKERATOSIS CONGENITA

Dyskeratosis congenita is a rare, inherited form of ectodermal dysplasia, characterized by reticulate skin pigmentation, mucosal leukoplakia, and nail dystrophy. Aplastic anemia occurs in at least 50% of patients with dyskeratosis congenita, usually during their teens, and cancer (predominantly squamous cell carcinoma) is seen in 10% of the patients during their twenties and thirties. The overall predicted median length of survival for patients with dyskeratosis congenita is 32 years, and death occurs from infection or malignancy. Treatment for patients with dyskeratosis congenita is at present unsatisfactory. For treatment of bone marrow failure, a combination of androgens and steroids may be tried. Transient responses to hematopoietic growth factors have been reported (erythropoietin, G-CSF, GM-CSF). Allogeneic sibling BMT has led to some engraftment, but rates of long-term survival have been poor. Compatible sibling donor BMT is still an experimental form of treatment for patients with dyskeratosis congenita, in contrast to patients with FA.

SHWACHMAN-DIAMOND SYNDROME

The Shwachman-Diamond syndrome consists of exocrine pancreatic insufficiency and neutropenia. Pancreatic insufficiency manifests in early infancy as steatorrhea and failure to thrive. Neutropenia occurs in early childhood, and recurrent skin infections and pneumonias may be present. Many patients develop anemia (15%), thrombocytopenia (7%), or both (20%). Physical examination reveals signs of malnutrition and short stature (50%), mental retardation (15%), and, in rare cases, dysmorphic facies, retinitis pigmentosa, syndactyly, and disordered skin pigmentation. Bone marrow cellularity is decreased in half the patients, the others showing an arrest of myeloid maturation. Chromosomes are normal, and there is no increased breakage after clastogenic stress. The malabsorption responds to treatment with oral pancreatic enzymes. Supportive care is given during infections (antibiotics, G-CSF, transfusions as needed). The projected median length of survival is 35 years for all patients with Shwachman-Diamond syndrome, and death is caused by hemorrhage or infection. There appears to be a malignant propensity in these patients, and acute leukemia has been reported. BMT has produced less than 50% survival in a small number of patients and is not strongly recommended.

SUMMARY

Severe aplastic anemia is more commonly acquired and idiopathic. The treatment of choice is matched related donor BMT, especially in children and young adults; survival rates exceed 90%. Immunosuppressive therapy offers a more than 70% overall remission rate in patients without a related matched donor and in older patients. High-dose cyclophosphamide may have potential as an immunosuppressive treatment, but larger trials are needed. Fanconi's anemia, dyskeratosis congenita, and Shwachman-Diamond syndrome are some of the inherited forms of aplastic anemia. Fanconi's anemia, by far the most common inherited AA, must be ruled out in all newly diagnosed cases of AA by chromosomal breakage studies of peripheral blood lymphocytes. There is a significant later risk of development of clonal disease such as acute myeloid leukemia, paroxysmal nocturnal hemoglobinuria, and myelodysplastic syndrome in idiopathic as well as inherited forms of AA. Solid tumors such as squamous cell carcinoma and liver tumors are also being seen in adults with FA. Patients with dyskeratosis congenita and Shwachman-Diamond syndrome moreover have a propensity for developing malignancies. Thus these inherited conditions (especially FA) must be kept in mind when young adults with refractory anemias or squamous cell carcinomas are evaluated.

IRON DEFICIENCY

method of
KENNETH R. BRIDGES, M.D.
Brigham and Women's Hospital
Boston, Massachusetts

Iron deficiency is a leading cause of anemia. In adults, the condition results almost exclusively from blood loss. Iron deficiency occasionally occurs in children because iron absorption fails to keep pace with the high demand created by neonatal and adolescent growth spurts. Body iron stores for women normally vary between 1 and 2 grams, whereas those of men average 3 to 4 grams. The liver is the source of most stored iron. Depletion of iron stores precedes a failure to produce iron-containing proteins—of most importance, hemoglobin. The two important stages of iron deficiency are thus (1) depletion of iron stores without anemia and (2) depletion of iron stores with anemia.

ETIOLOGY OF IRON DEFICIENCY

Treatment of iron deficiency cannot be efficiently undertaken until the cause of the iron deficit is discovered. Blood loss into the gastrointestinal tract is by far the most common cause of iron deficiency. A cautious physician should be aware of a couple of other possibilities, however.

Abnormal Iron Uptake from the Alimentary Tract

Impaired iron absorption from the gastrointestinal tract rarely causes iron deficiency. One etiology of increasing importance to internists is a high gastric pH. A high gastric pH reduces the solubility of inorganic iron, impeding its absorption. Surgical interventions, such as vagotomy or hemigastrectomy for peptic ulcer disease, were formerly the major causes of impaired gastric acidification. Iron deficiency developed as a secondary event. Today, the histamine H_2 blockers (such as cimetidine [Tagamet]) and the more recently introduced acid pump inhibitors (e.g., omeprazole [Prilosec]), used to treat peptic ulcer disease and acid reflux, are the most common causes of defective iron absorption. Although these medications infrequently produce iron deficiency, their widespread use means that most internists will encounter the problem at some time.

Peptic ulcer disease can itself produce iron deficiency as a result of bleeding into the gastrointestinal tract (described later). The use of agents that block gastric acidification and iron absorption by people whose iron stores are low or absent is an efficient means of producing iron deficiency anemia.

Some disorders disrupt the integrity of the enteric mucosa, thereby hampering iron absorption. Inflammatory bowel disease, such as Crohn's disease, can cause iron deficiency anemia by this mechanism. The diagnosis of Crohn's disease as the cause of iron deficiency is a straightforward exercise, however.

Celiac disease (nontropical sprue) can also impair iron absorption. Unlike Crohn's disease, celiac disease often disrupts iron absorption while manifesting only subtle clinical signs. Some patients with mild celiac disease experience minor symptoms such as bloating after eating a meal rich in gluten, such as bran cereal. Nonetheless, the condition sometimes substantially impairs iron absorption. Iron deficiency anemia occurs often when a concurrent predisposing condition exists, such as chronic use of aspirin or nonsteroidal anti-inflammatory agents. Some patients with deranged iron absorption lack gross or even histologic changes in the structure of the bowel mucosa. A gluten-free diet improves bowel function in many such patients, with secondary correction of the anemia.

Blood Loss

The gastrointestinal tract is both the site of iron uptake and the most common location of blood loss. This organ is unrivaled as a potential setting for occult bleeding. In adults, the chief cause is a gastrointestinal malignancy. A work-up of the gastrointestinal tract for malignancy is mandatory in men with iron deficiency anemia. Peptic ulcer disease, hiatal hernia, or other benign lesions are the most common findings. However, a malignancy must be searched for.

The problem is complicated in women, in whom menstruation is a physiologic source of blood loss. Iron deficiency anemia occurs in about 2% of premenopausal women solely as a result of menstruation. Iron stores are depleted in the absence of anemia in about 10% of premenopausal women. The key dilemma is whether to pursue the issue of gastrointestinal blood loss (with malignancy as the key target), despite menstruation as the probable cause.

No clear-cut answer to this quandary exists. Each situation must be considered carefully on it own merit. For example, in a 36-year-old mother of three children with a history of menorrhagia, gynecologic and obstetric blood loss alone are sufficient to explain iron deficiency anemia. Although gastrointestinal bleeding from a carcinoma could also contribute to the anemia, the chance of this is extremely small. Should stool guaiac cards over several days